PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference LABO-005/01WO311815	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/IB2008/053711	International filing date (*day/month/year*) 21 March 2008 (21.03.2008)	Priority date (*day/month/year*) 21 March 2007 (21.03.2007)
International Patent Classification (IPC) (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ALMIRALL, S.A.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis*.2).

	Date of issuance of this report 22 September 2009 (22.09.2009)
The International Bureau of WIPO 34, chemin des Colombettes CH-1211 Geneva 20, Switzerland	Authorized officer Ellen Moyse
Facsimile No. +41 22 338 82 70	e-mail: pt02.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/057911	21.03.2008	21.03.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/14 C07D403/04 C07D405/14 A61K31/506 A61P3/04 A61P9/00 A61P11/00 A61P25/00 A61P37/00

Applicant
NEUROCRINE BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☑ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

   If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office · Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 · 0 Fax: +49 30 25901 · 840	see form PCT/ISA/210	Rulet, Jacques Telephone No. +49 30 25901 332

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-9, 16-20 all partially

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-9, 16-20 all partially

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☑ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☑ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☑ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☑ the parts relating to claims Nos. 1-9, 16-20 all partially and 10-15 complete

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12,15
	No:	Claims	1-11,*3,14,16-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

A non-unity objection has been raised during the search stage. The Applicant has not paid extra fees, therefore no search report has been issued for the subject-matter of the claims 1-9 and 16-20 when compounds of claim 1 wherein R^2 is isoquinoline, dihydroisoquinoline or tetrahydroisoquinoline are concerned.
Consequently no opinion will be given for the subject-matter of these claims.

Re Item IV.

1. The ISA found multiple inventions (two) in this application which are not so linked as to form a single general inventive concept (Rule 13.1 PCT) as follow:

Invention 1 (claims 1-9, 16-20 all partially and 10-15 complete):

Provision of compounds of formula (I) of claim 1 wherein R^2 is phenyl or pyridiyl, wherein the phenyl or pyridyl ring is substituted by 1 to 4 R^4 groups, useful in the treatment of disorders which benefit from the inhibition of adenosine receptors like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsity, diabetes mellitus, Parkinson's disease, etc....

Invention 2 (claims 1-9 and 16-20 all partially):

Provision of compounds of formula (I) of claim 1 wherein R^2 is isoquinoline, dihydroisoquinoline or tetrahydroisoquinoline ring, useful in the treatment of disorders which benefit from the inhibition of adenosine receptors like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsity, diabetes mellitus, Parkinson's disease, etc....

2. The International Examination Authority (IEA) fully supports the non-unity objection of the ISA, since the two inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

According to the description, see especially page 1, first paragraph as well as page 3, line 30 to page 4, line 6, the problem underlying the present application is the provision of compounds useful in the treatment of disorders which benefit from the inhibition of adenosine receptors, like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsity, diabetes mellitus, Parkinson's disease, etc....

The proposed solution is the provision of 2,6 substituted-4-aminopyridimidines derivatives of formula (I) acccording to claim 1 having as common structural feature the structure given by formula (I) of claim 1.

2,6 substituted-4-aminopyrimidine derivatives having this common structural feature and useful in the treatment of Parkinson's disease or Alzheimer's disease have already been disclosed in WO-A-2005/058883 (see especially claims 1, 7, 8, 14 and examples 85 to 96, as well as present claim 1 when R4 is hydrogen (m, n, p is 0 and R5 is hydrogen) or EP0459830 (see especially claim 3, lines 20, 21 and page 2, lines 1-11). This common structural feature is therefore not new.

It is pointed out that the mechanism of action of the compounds cannot be regarded as a technical feature since it represents an inherent property of the compounds. It is stressed that the mere explanation of an effect obtained when using a compound in a known composition even if the effect was not known to be due to this compound in the known composition, cannot confer novelty on a known process if the skilled person was already aware of the occurence of the desired effect (e.g. treatment of pain). In orther words, the discovery of the mechanism of action of the compounds does not render the use of those compounds novel.

The problem underlying the invention can be therefore redefined as the provision of further 2,6 substituted-4-aminopyridimidines derivatives derivatives useful in treating of disorders which benefit from the inhibition of adenosine receptors like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsily, diabetes mellitus, Parkinson's disease, etc....
The inventions 1 and 2 mentioned above are different solutions to this problem, which do

not share any novel common feature. Due to the fact that compounds having the common structural feature useful for treating disorders which benefit from the inhibition of adenosine receptors like Alzheimer's disease are already known from the prior art and due to the fact that no other technical features can be regarded as special technical features in the sense of rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the 2 inventions claimed in the present application in the sense of rule 13.1 PCT.

Re Item V.

1 Claims 19 and 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.
The patentability can also dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

2 Reference is made to the following documents:

D1: WO 2005/058883 A (ALMIRALL PRODESFARMA SA [ES]) 30 June 2005
D2: EP-A-0 459 830 (WELLCOME FOUND [GB]) 4 December 1991
D3: WO 2006/110884 A (NEUROCRINE BIOSCIENCES INC [US]) 19 October 2006
D4: WO 2004/048365 A (CHIRON CORP [US]10 June 2004
D5: EP-A-0 407 899 (HOECHST AG [DE]) 16 January 1991 (1991-01-16)
D6: JP 54 117029 A (HOKKO CHEMICAL INDUSTRY CO., LTD) 11 September 1979
D7: JP 54 147921 A (HOKKO CHEMICAL INDUSTRY CO., LT.) 19 November 1979
D8: JP 54 115384 A (HOKKO CHEMICAL INDUSTRY CO., LTD) 7 September 1979
D9: Beilstein Database, Accession no. 298388

3 Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-11,13, 14, 16-20 is considered to be not novel over the prior art D1-D9 in the sense of Article 33(2) PCT for the following reasons:

Document D1 discloses compounds (see examples 85-88, 90-93, 95, 96) falling under the scope of present claims 1-11 as well as a family of compounds defined by a general structural formula which overlaps with the family of compounds of general formula (I) of present claim 1; see D1, especially the definitions of R^1 in claims 1, 4-6, R^2 in claims 7, 8 and R^3 in claim 1.
It is pointed out that the compounds of D1 are also useful in the treatment of disorders which benefit from the inhibition of adenosine receptors, like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsity, diabetes mellitus, Parkinson's disease, etc....
Document D2 describes two compounds (see claim 3, lines 20, 21) falling under the scope of present formula (I) also useful for the treatment of neurodegenerative disorders like Alzheimer's disease; thus rendering the subject-matter of claims 1, 13, 14, 16-20 not novel.
Document D3 describes two intermediate compounds (no. 13, 15) which fall under the scope of present claims 1, 2,4, 6, 7, 10 and 11.
Document D4 refers to specific compounds (see examples 73-75, 121) falling under the scope of present claims 1, 13 and 14 as well as a family of compounds defined by a general structural formula which overlaps with the family of compounds of general formula (I) of present claim 1; see D4, claim 1 as well as pharmaceutical compositions thereof.
Documents D5-D8 disclose specific compounds as well as family of compounds defined by general structural formulae which overlap with the family of compounds of general formula (I) of present claim 1 (see the relevant passages cited in the search report respectively) useful as pesticides.
Document D9 refers to a compound falling under the scope of present claim 1 when R^1, R^2 are pyridyl and R^3 is hydrogen.

4 In filing new claims, the Applicant should submit a new set of claims the subject-matter of which is clearly distinguished from the prior art D1-D9 and for which the presence of an inventive step within the meaning of Art. 33(1)-(3) may be substantiated.

It should be made clear which features distinguish the subject-matter of these new claims from each cited documents and which objective technical problem is solved by these features in an **unexpected** manner.
A technical effect which justifies the selection of the claimed compounds should be one which can be fairly assumed by **substantially all the selected compounds**, and if it is evident that the number of compounds claimed, due to speculative expressions like "heterocycle" or "heterocyclic ring" used in claim 1, is such that it is inherently unlikely that all of them, or at least substantially all of them, will possess the promised activity, than the burden of proof of that fact, i. e. the possession of that activity, can rest only upon the shoulders of the person alleging it.

Re Item VIII.

1. The term "lower" used in claims 1, 3 and 7 has no generally accepted meaning in the art and is regarded as unclear, since the higher limit of carbon atoms is not unambiguously defined (Art. 6 PCT).

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/057911	21.03.2008	21.03.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/14 C07D403/04 C07D405/14 A61K31/506 A61P3/04 A61P9/00 A61P11/00 A61P25/00 A61P37/00

Applicant
NEUROCRINE BIOSCIENCES, INC.

1. This opinion contains indications relating to the following items:

   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☑ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

   If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office · Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 · 0 Fax: +49 30 25901 · 840	see form PCT/ISA/210	Rulet, Jacques Telephone No. +49 30 25901 332

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-9, 16-20 all partially

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-9, 16-20 all partially

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☑ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☑ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☑ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☑ the parts relating to claims Nos. 1-9, 16-20 all partially and 10-15 complete

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12,15
	No:	Claims	1-11,*3,14,16-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

A non-unity objection has been raised during the search stage. The Applicant has not paid extra fees, therefore no search report has been issued for the subject-matter of the claims 1-9 and 16-20 when compounds of claim 1 wherein R^2 is isoquinoline, dihydroisoquinoline or tetrahydroisoquinoline are concerned.
Consequently no opinion will be given for the subject-matter of these claims.

Re Item IV.

1. The ISA found multiple inventions (two) in this application which are not so linked as to form a single general inventive concept (Rule 13.1 PCT) as follow:

Invention 1 (claims 1-9, 16-20 all partially and 10-15 complete):

Provision of compounds of formula (I) of claim 1 wherein R^2 is phenyl or pyridiyl, wherein the phenyl or pyridyl ring is substituted by 1 to 4 R^4 groups, useful in the treatment of disorders which benefit from the inhibition of adenosine receptors like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsity, diabetes mellitus, Parkinson's disease, etc....

Invention 2 (claims 1-9 and 16-20 all partially):

Provision of compounds of formula (I) of claim 1 wherein R^2 is isoquinoline, dihydroisoquinoline or tetrahydroisoquinoline ring, useful in the treatment of disorders which benefit from the inhibition of adenosine receptors like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsity, diabetes mellitus, Parkinson's disease, etc....

2. The International Examination Authority (IEA) fully supports the non-unity objection of the ISA, since the two inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

According to the description, see especially page 1, first paragraph as well as page 3, line 30 to page 4, line 6, the problem underlying the present application is the provision of compounds useful in the treatment of disorders which benefit from the inhibition of adenosine receptors, like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsity, diabetes mellitus, Parkinson's disease, etc....

The proposed solution is the provision of 2,6 substituted-4-aminopyridimidines derivatives of formula (I) acccording to claim 1 having as common structural feature the structure given by formula (I) of claim 1.

2,6 substituted-4-aminopyrimidine derivatives having this common structural feature and useful in the treatment of Parkinson's disease or Alzheimer's disease have already been disclosed in WO-A-2005/058883 (see especially claims 1, 7, 8, 14 and examples 85 to 96, as well as present claim 1 when R4 is hydrogen (m, n, p is 0 and R5 is hydrogen) or EP0459830 (see especially claim 3, lines 20, 21 and page 2, lines 1-11). This common structural feature is therefore not new.

It is pointed out that the mechanism of action of the compounds cannot be regarded as a technical feature since it represents an inherent property of the compounds. It is stressed that the mere explanation of an effect obtained when using a compound in a known composition even if the effect was not known to be due to this compound in the known composition, cannot confer novelty on a known process if the skilled person was already aware of the occurence of the desired effect (e.g. treatment of pain). In orther words, the discovery of the mechanism of action of the compounds does not render the use of those compounds novel.

The problem underlying the invention can be therefore redefined as the provision of further 2,6 substituted-4-aminopyridimidines derivatives derivatives useful in treating of disorders which benefit from the inhibition of adenosine receptors like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsily, diabetes mellitus, Parkinson's disease, etc....
The inventions 1 and 2 mentioned above are different solutions to this problem, which do

not share any novel common feature. Due to the fact that compounds having the common structural feature useful for treating disorders which benefit from the inhibition of adenosine receptors like Alzheimer's disease are already known from the prior art and due to the fact that no other technical features can be regarded as special technical features in the sense of rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the 2 inventions claimed in the present application in the sense of rule 13.1 PCT.

Re Item V.

1 Claims 19 and 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.
The patentability can also dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

2 Reference is made to the following documents:

D1: WO 2005/058883 A (ALMIRALL PRODESFARMA SA [ES]) 30 June 2005
D2: EP-A-0 459 830 (WELLCOME FOUND [GB]) 4 December 1991
D3: WO 2006/110884 A (NEUROCRINE BIOSCIENCES INC [US]) 19 October 2006
D4: WO 2004/048365 A (CHIRON CORP [US]10 June 2004
D5: EP-A-0 407 899 (HOECHST AG [DE]) 16 January 1991 (1991-01-16)
D6: JP 54 117029 A (HOKKO CHEMICAL INDUSTRY CO., LTD) 11 September 1979
D7: JP 54 147921 A (HOKKO CHEMICAL INDUSTRY CO., LT.) 19 November 1979
D8: JP 54 115384 A (HOKKO CHEMICAL INDUSTRY CO., LTD) 7 September 1979
D9: Beilstein Database, Accession no. 298388

3 Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-11,13, 14, 16-20 is considered to be not novel over the prior art D1-D9 in the sense of Article 33(2) PCT for the following reasons:

Document D1 discloses compounds (see examples 85-88, 90-93, 95, 96) falling under the scope of present claims 1-11 as well as a family of compounds defined by a general structural formula which overlaps with the family of compounds of general formula (I) of present claim 1; see D1, especially the definitions of R^1 in claims 1, 4-6, R^2 in claims 7, 8 and R^3 in claim 1.
It is pointed out that the compounds of D1 are also useful in the treatment of disorders which benefit from the inhibition of adenosine receptors, like Alzheimer's disease, dyskinesia, ischemia, arrythmis, acute renal failure, autoimmune diseases, inflammatory bowel diseases, asthma, obsity, diabetes mellitus, Parkinson's disease, etc....
Document D2 describes two compounds (see claim 3, lines 20, 21) falling under the scope of present formula (I) also useful for the treatment of neurodegenerative disorders like Alzheimer's disease; thus rendering the subject-matter of claims 1, 13, 14, 16-20 not novel.
Document D3 describes two intermediate compounds (no. 13, 15) which fall under the scope of present claims 1, 2,4, 6, 7, 10 and 11.
Document D4 refers to specific compounds (see examples 73-75, 121) falling under the scope of present claims 1, 13 and 14 as well as a family of compounds defined by a general structural formula which overlaps with the family of compounds of general formula (I) of present claim 1; see D4, claim 1 as well as pharmaceutical compositions thereof.
Documents D5-D8 disclose specific compounds as well as family of compounds defined by general structural formulae which overlap with the family of compounds of general formula (I) of present claim 1 (see the relevant passages cited in the search report respectively) useful as pesticides.
Document D9 refers to a compound falling under the scope of present claim 1 when R^1, R^2 are pyridyl and R^3 is hydrogen.

4 In filing new claims, the Applicant should submit a new set of claims the subject-matter of which is clearly distinguished from the prior art D1-D9 and for which the presence of an inventive step within the meaning of Art. 33(1)-(3) may be substantiated.

It should be made clear which features distinguish the subject-matter of these new claims from each cited documents and which objective technical problem is solved by these features in an **unexpected** manner.
A technical effect which justifies the selection of the claimed compounds should be one which can be fairly assumed by **substantially all the selected compounds**, and if it is evident that the number of compounds claimed, due to speculative expressions like "heterocycle" or "heterocyclic ring" used in claim 1, is such that it is inherently unlikely that all of them, or at least substantially all of them, will possess the promised activity, than the burden of proof of that fact, i. e. the possession of that activity, can rest only upon the shoulders of the person alleging it.

Re Item VIII.

1. The term "lower" used in claims 1, 3 and 7 has no generally accepted meaning in the art and is regarded as unclear, since the higher limit of carbon atoms is not unambiguously defined (Art. 6 PCT).